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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/933,115	08/20/2001	Paul B. Fisher	A34466 (070050.1618)	7088

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/933,115	FISHER, PAUL B.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *43-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12/8/03 12/10/03 12/3/01
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This Action is in response to the communication filed on 12/3/03. Claims 1-50 are currently pending in the application and are addressed herein.

Election/Restrictions

Applicant's election with traverse of Group I (and species: antisense molecules) in the communication filed 12/3/03 is acknowledged. The traversal is on the ground(s) that there is no search burden for searching Group III with Group I. Applicants also traverse the election of species requirement and argue that the 2 groups of species should be combined into a single group because it would prohibit applicants from pursuing claims drawn to the working example. Applicant's arguments are found partially persuasive. Specifically, the election of species requirement is adjusted as suggested, and the election of the species antisense molecules is acknowledged. However, with respect to the rejoinder of Groups I and III, applicant's arguments are not persuasive. As indicated in the previous Office Action, the search required for Group III is not co-extensive with the search for Group I.

2. Claims 43-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper filed 12/3/03.

3. Claims 1-42 are examined herein.

Claim Rejections - 35 USC § 112, second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 5-9, 15-19, 25-29 35-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Regarding claims 5, 15, 25 and 35, the phrase "for example" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Claims 6-9, 16-19, 26-29 and 36-39 are dependent claims and are, as such, rejected for the same reason.

Claim Rejections - 35 USC § 112, first paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

9. The instant claims are drawn to methods of inhibiting proliferation and/or inducing apoptosis in cancer cells by increasing the amount of MDA-7 and decreasing the activity of RAS in the cancer cells (e.g., see claims 1, 21, 31). The claimed methods, however, do not set forth any method steps for completing BOTH increasing the amount of MDA-7 and decreasing RAS

activity in the cancer cells. Therefore, applicants have not adequately indicated how to make/use the claimed invention. It is noted that dependent claims (e.g., 2-4) indicate steps by which the amount of MDA-7 can be increased (e.g., using a nucleic acid encoding MDA-7). It is also acknowledged that dependent claims (e.g., 5-10) indicate steps by which the activity of RAS can be decreased (e.g., including using an antisense molecules, including a vector which expresses antisense molecules and MDA-7). However, the methods steps for increasing MDA-7 (e.g., claims 2-5) and the method steps for decreasing RAS activity (e.g., claim 5-10) all depend on claim 1. Therefore, the claims encompass a method for increasing MDA-7 and decreasing RAS activity by using steps the EITHER increase the amount of MDA-7 or steps that decrease RAS activity. None of the instant claims explicitly sets forth the steps for BOTH increasing MDA-7 and decreasing RAS activity. It is acknowledged that certain claims (e.g., claim 9) are drawn to the method(s) wherein RAS activity is decreased by administering a viral vector encoding an antisense molecule and MDA-7 in expressible form. However, this claim (claim 9) depends on the base claim (e.g., claim 1); therefore, claim 9 is only drawn to:

> A method of inhibiting proliferation and/or inducing apoptosis in cells by increasing the amount of MDA-7 and decreasing the activity of RAS in the cancer cells wherein RAS activity is decreased by administering a viral vector encoding an antisense molecule and MDA-7 in expressible form.

In this example, there is no clear and explicit indication of the method steps used to increase the amount of MDA-7 in the cells.

It is respectfully pointed out that amending the claims to clearly indicate the steps by which both increasing MDA-7 and decreasing RAS activity is achieved would obviate this rejection. For instance, providing a claim that read:

> A method of inhibiting proliferation and/or inducing apoptosis in cancer cells by increasing the amount of MDA-7 and decreasing the activity of RAS in the cancer cells by administering a viral vector that encodes and expresses an antisense RAS molecule in said cancer cells, and wherein said viral vector further encodes and expresses MDA-7 in said cancer cells.
> would obviate this rejection.

10. Claims 1-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

11. The instant claims are drawn to methods of inhibiting proliferation of cancer cells by increasing the amount of MDA-7 and decreasing the activity of RAS in the cancer cells (e.g., see claims 1, 21, 31). It is noted that the claims are very broad and encompass any molecules that increase MDA-7 and any molecule that decreases RAS activity in a cell. Furthermore, claims 1-40 encompass any molecules that can increase MDA-7 as well as decrease RAS activity in a cell. Considering the breadth of claims, the claims encompass a genus of molecules indefinite in size, but which may encompass possibly thousands of different molecules, considering every molecule that could possibly directly, or even indirectly, increase MDA-7 and/or decrease RAS activity in a cell.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical

properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164).

As mentioned above, the claims encompass a genus of molecules that could include possibly thousands of different species (molecules) considering every molecule that could possibly increase MDA-7 and/or decrease RAS activity in a cell. It is respectfully pointed out that the indicated genus would encompass molecules which have not yet been identified, as well as molecules having unrelated chemical structures which function through different biological pathways. For instance the genus of molecules would encompass antisense nucleic acid molecules, small organic molecules, polypeptides, hormones, transcription factors, expression inhibitors, etc.

The specification only discloses certain specific molecules which can either increase the amount of MDA-7 in a cell or decrease RAS activity in a cell. There is no description of any molecules that can both increase MDA-7 and decrease RAS activity in a cell. Furthermore, with respect to molecules that increase MDA-7 in a cell, the specification appears to only disclose two molecules, a nucleic acid which expresses MDA-7 and MDA-7 protein itself; both of which could be administered to a cell, resulting in increasing the amount of MDA-7 in the cell. With respect to the genus of molecules that inhibit RAS activity in a cell, the specification only explicitly describes certain molecules that directly inhibit the expression of RAS in a cell. Specifically, the disclosed molecules which can inhibit RAS activity in a cell are **RAS-specific** antisense molecules, ribozymes, triplex-forming molecules. It is respectfully pointed out that the claims encompass inhibiting RAS activity by administering any antisense molecule (e.g., see

claim 6). The specification describes dominant-negative RAS inhibitor and farnesyl transferase as inhibitors of RAS activity.

However, considering the breadth of the claims and the limited number of species disclosed, the specification has not adequately described the genus encompassed by the claims. For instance, the specification has not described any molecules that can BOTH increase MDA-7 and decrease RAS activity in a cell. Furthermore, considering the claims encompass molecules which have not yet been identified including molecules which have unrelated chemical structures and biological functions, the few species disclosed is not representative of the entire genus encompassed by the claims.

12. Additionally, claims 1-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, in view of the written description rejection above. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As mentioned above, the claims encompass molecules for which there is insufficient written description provided. Without a clear indication of the molecules encompassed by the claims one of skill in the art would not know how to make or use the claimed invention without performing an undue amount of additional experimentation.

13. Claims 1-42 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for inhibiting proliferation and/or inducing apoptosis in pancreatic cancer cells expressing K-ras by directly administering to said pancreatic cancer cells a composition comprising:

(i) a nucleic acid that encodes and expresses MDA-7 in cancer cells, and

or

(ii) an antisense nucleic acid molecule that specifically hybridizes to a nucleic acid encoding K-ras under stringent conditions,

does not reasonably provide enablement for the full scope encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to methods of inhibiting proliferation and/or inducing apoptosis in cancer cells. Therefore the general nature of the Invention is cancer therapy. Furthermore, the claims encompass administering a nucleic acid which encodes and expresses a therapeutic protein in a cancer cell, as well as an antisense molecule. Therefore, the nature of the claims is more specifically cancer gene therapy, including antisense therapy.

The breadth of the claims

As mentioned above, the claims are very broad. The most general claims encompass methods of increasing the amount of MDA-7 in a cancer cell, and decreasing the activity of RAS in said cancer cell using any method steps and any molecules (e.g., see claim 1). Furthermore, the claims encompass administering molecules such as vectors and nucleic acids to subjects wherein the molecules are administered by no particular route of administration, and as such, encompass general systemic administration of the molecules. The claims are broad enough to encompass administering a single molecule to increase MDA-7 and decrease RAS activity in cells as well as administering more than molecule. The claims indicate the any anti-RAS agent, including an antisense molecule, however, there is no indication that the anti-RAS antisense molecule is an antisense oligonucleotide the specifically hybridizes to RAS under stringent conditions. Therefore, the claims could encompass administering any antisense molecule. Additionally the claims are drawn to "treating" cancer. "Treating" cancer is a very broad concept and encompasses inhibiting cell growth, inducing cancer cell death, completely curing cancer and inhibiting any future occurrence of cancer.

The unpredictability of the art and the state of the prior art

As indicated above, the claims are generally drawn to combination cancer therapy comprising gene therapy and antisense therapy. Both gene therapy and antisense therapy encompass administering therapeutic nucleic acids to a subject in order to treat cancer. However, at the time of invention, the relevant art recognizes several problems associated with the administration of nucleic acids to subjects, and specifically recognized problems with administering nucleic acids for treating cancer.

For instance, it is well established in the art that delivery is one of the key problems of gene therapy. Regarding gene therapy in general, Anderson (Nature 1998; 392(suppl):25-30) teaches,

> "The challenge is to develop gene therapy as an efficient and safe drug delivery system. The goal is more difficult to achieve than many investigators had predicted... The human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome. (See p. 25, second paragraph). The ultimate goal of gene therapy research is the development of vectors that can be injected, will target specific cells, will result in safe and efficient gene transfer into a high percentage of those cells, will insert themselves into appropriate regions of the genome (or will persist as stable episomes), will be regulated be either by administered agents or by the body's own physiological signals, will be cost effective and will cure disease." (See p. 30, first paragraph).

Crystal (Science 1995; 270:404-410) also indicates some of the problems regarding gene therapy in general. Specifically, regarding the obstacles of human gene transfer, Crystal teaches, "The [gene transfer] vector (should) be specific for its target, not recognized by the immune system..." (See p. 409, column 2 under "The perfect vector").

Finally, regarding the delivery of gene therapy vectors to tumors, but applicable to the specific delivery of all gene therapy molecules, Greco (Frontiers in Biosci. 2002; 7:d1516-1524) teaches,

> The administration of gene therapy vectors requires that they be not only targeted, but also protected from degradation, sequestration or immune attack, in order to reach the appropriate sites for transfection. Although some success has been reported for naked DNA, efficient delivery has been restricted to intratumoral injection. (See p. 1517, paragraph bridging columns 1-2).

Indicating that direct delivery of the therapeutic nucleic acid to the desired site of transfection is critical for delivering the nucleic acid to the appropriate cells.

Additionally, there is no master drug known in the art which can effectively "treat" cancer to the extent that it completely cures the subject of cancer and prevents any future

occurrence of cancer. Therefore, without evidence to the contrary, it is highly unlikely that any drug will completely cure cancer and prevent any future occurrence.

There are also no single compounds found in the art which can increase MDA-7 in a cell and inhibit RAS activity in a cell.

Regarding antisense therapy. It is acknowledged that the prior art recognizes a number of different antisense molecules which can inhibit RAS activity in a cell, including molecules which are cancer therapies. However, all of the known antisense molecules which inhibit RAS activity in a cell are antisense molecules which specifically hybridize to nucleic acids encoding RAS under stringent conditions. There are no antisense molecules recognized in the art which inhibit RAS activity, but which do not specifically hybridize to RAS.

Working Examples and Guidance in the Specification

The working examples included in the specification indicate the administration of a combination of an adenoviral vector that encodes and expresses MDA-7 and an antisense nucleic acid that specifically hybridizes to a nucleic acid encoding RAS, synergistically inhibited the growth of human pancreatic carcinoma cells when the composition was directly administered to these specific cancer cells. The effect was seen only in pancreatic cancer cells that had the K-ras mutant form of ras (not in any other pancreatic cancer cell line). The effect of the combination treatment on pancreatic cancer cells is synergistic because the effect of the combination is greater than the sum of both treatments individually (See Figures 5-6). Several different antisense molecules were tested, including antisense molecules that specifically hybridized to K-ras as well as "scrambled" and "mismatched" antisense sequences; however, only the antisense molecules specific for K-ras demonstrated the anti-cancer effect. The anti-cancer effect of the

combination was demonstrated in cancer cell lines (in vitro) as well as in tumors in mice (wherein the composition was administered directly to the tumors).

Quantity of Experimentation

Considering the breadth of the claims, an enormous amount of experimentation would have to be performed in order for one of skill in the art to be able to practice the claimed invention to the full scope encompassed by the claims. For instance, additional experimentation would be required with respect to the therapeutic compounds encompassed by the claims, but not adequately described. Further experimentation would be required to overcome the art-recognized problems associated with systemic administration of nucleic acids for cancer therapy. And finally, additional experimentation would be required in order to show that the methods could be used to treat any type of cancer, including non-pancreatic cancers (and pancreatic cancers not having the K0ras mutation), and that the treatment would result in the curing of the cancer as well as the permanent prevention of any future cancer.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the breadth of the claims, the high degree of unpredictability of gene therapy recognized in the art, the limited working examples and guidance in the specification, and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed invention is undue.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (571) 272-0756. The examiner can normally be reached on M-F (8:00-5:30) with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVE T. NGUYEN
PRIMARY EXAMINER

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Art Unit 1635